UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606** Master Case No. 15-2606 (RBK/JS) Hon. Robert B. Kugler, U.S.D.J. Hon. Joel Schneider, U.S.M.J.
THIS DOCUMENT RELATES TO ALL CASES	

DEFENDANTS' BRIEF IN SUPPORT OF MOTION TO EXCLUDE TESTIMONY OF DR. DANIEL LEFFLER AND DR. BENJAMIN LEBWOHL

DRINKER BIDDLE & REATH LLP
A Delaware Limited Liability Partnership
600 Campus Drive
Florham Park, New Jersey 07932-1047
(973) 549-7000
Attorneys for Defendants Daiichi Sankyo, Inc., Daiichi Sankyo US Holdings, Inc., Daiichi Sankyo Company, Ltd., Forest Laboratories, Inc., now known as Forest Laboratories, LLC, Forest Pharmaceuticals, Inc., and Forest Research Institute, Inc.

TABLE OF CONTENTS

Page

PRELIMINARY STATEMENT 1

STATEMENT OF FACTS 1

LEGAL ARGUMENT 1

I. DRS. LEFFLER AND LEBWOHL'S OPINION THAT OLMESARTAN CAN CAUSE SPRUE-LIKE ENTEROPATHY IS NOT GROUNDED IN EXISTING SCIENCE 4

A. Speculation Concerning Misdiagnosis/Underdiagnosis 9

B. Unsupported and Uncertain Diagnostic Criteria 10

II. DRS. LEFFLER AND LEBWOHL IMPROPERLY DUCK THE WEIGHT OF EPIDEMIOLOGICAL DATA 15

A. The ROADMAP Study 17

B. The Greywoode Study 20

C. The Lagana Study 21

D. The Padwal Study 22

III. DRS. LEFFLER AND LEBWOHL CONCEDE THERE IS NO DOSE RESPONSE RELATIONSHIP BETWEEN OLMESARTAN AND GASTROINTESTINAL DISEASE 25

IV. THE MEDICAL LITERATURE DOES NOT SUPPORT A PLAUSIBLE BIOLOGICAL MECHANISM OF ACTION 28

V. DRS. LEFFLER AND LEBWOHL'S OPINION THAT ADVERSE EVENT REPORTS AND CASE REPORTS SUPPORT GENERAL CAUSATION IS NOT RELIABLE 34

CONCLUSION 40

TABLE OF AUTHORITIES

Page(s)

CASES

Allison v. McGhan Med. Corp.,
184 F.3d 1300 (11th Cir. 1999) 37

In re Baycol Prods. Litig.,
532 F. Supp. 2d 1029 (D. Minn. 2007).....10

In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.,
524 F. Supp. 2d 1166 (N.D. Cal. 2007).....15

Brumbaugh v. Sandoz Pharm. Corp.,
77 F. Supp. 2d 1153 (D. Mont. 1999).....4, 34

Caraker v. Sandoz Pharms. Corp.,
188 F. Supp. 2d 1026 (S.D. Ill. 2001).....22

Carl v. Johnson & Johnson,
No. ATL-L-6546-14 (N.J. Sup. Sept. 2, 2016), slip op. (appeal
pending) 24, 26

Claar v. Burlington N. R.R. Co.,
29 F.3d 499 (9th Cir. 1994) 9

Concord Boat Corp. v. Brunswick Corp.,
207 F.3d 1039 (8th Cir. 2000) 3

Daubert v. Merrell Dow Pharms., Inc.,
509 U.S. 579 (1993).....*passim*

DeLuca v. Merrell Dow Pharms., Inc.,
791 F. Supp. 1042 (D.N.J. 1992).....35

Doe v. Ortho-Clinical Diagnostics, Inc.,
440 F. Supp. 2d 465 (M.D.N.C. 2006) 33

Ervin v. Johnson & Johnson, Inc.,
No. 2:04-cv-0205, 2006 WL 1529582 (S.D. Ind. May 30, 2006),
aff'd 492 F.3d 901 (7th Cir. 2007).....35, 36

Gen. Elec. Co. v. Joiner,
522 U.S. 136 (1997).....25

Glastetter v. Novartis Pharms. Corp.,
252 F.3d 986 (8th Cir. 2001).....11, 30

Hendrix v. Evenflo Co.,
255 F.R.D. 568 (N.D. Fla. 2009).....29

Hollander v. Sandoz Pharms. Corp.,
95 F. Supp. 2d 1230 (W.D. Okla. 2000).....11

Kilpatrick v. Breg, Inc.,
No. 08-10052-CIV, 2009 WL 2058384 (S.D. Fla. June 25, 2009).....8

Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999).....21, 40

Lennon v. Norfolk & W. Ry. Co.,
123 F. Supp. 2d 1143 (N.D. Ind. 2000).....14, 15

Lust v. Merrell Dow Pharm., Inc.,
89 F.3d 594 (9th Cir. 1996).....3, 16, 24

McClain v. Metabolife Int'l, Inc.,
401 F.3d 1233 (11th Cir. 2005).....33, 35

Meister v. Med Eng'g Corp.,
267 F.3d 1123 (D.C. Cir. 2001).....19

In re Methyl Tertiary Butyl Ether (MTBE) Prods. Liab. Litig.,
593 F. Supp. 2d 549 (S.D.N.Y. 2008).....24, 25

Miller v. Pfizer, Inc.,
356 F.3d 1326 (10th Cir. 2004).....4, 20, 34

In re Paoli R.R. Yard PCB Litig.,
35 F.3d 717 (3d Cir. 1994).....2, 14, 25

Pick v. Am. Med. Sys., Inc.,
958 F. Supp. 1151 (E.D. La. 1997).....8

In re Propulsid Prods. Liab. Litig.,
261 F. Supp. 2d 603 (E.D. La. 2003).....8

Rains v. PPG Indus., Inc.,
361 F. Supp. 2d 829 (S.D. Ill. 2004).....24

Rider v. Sandoz Pharms. Corp.,
295 F.3d 1194 (11th Cir. 2002) 11

Rosen v. Ciba-Geigy Corp.,
78 F.3d 316 (7th Cir. 1996) 27, 28

Siharath v. Sandoz Pharm. Corp.,
131 F. Supp. 2d 1347 (N.D. Ga. 2001).....36

Turner v. Iowa Fire Equip. Co.,
229 F.3d 1202 (8th Cir. 2000) 13, 14

United Soldo v. Sandoz Pharm. Corp.,
244 F. Supp. 2d 434 (W.D. Pa. 2003).....27

Weisgram v. Marley Co.,
528 U.S. 440 (2000).....3

Zenith Elecs. Corp. v. WH-TV Broadcasting Corp.,
395 F.3d 416 (7th Cir. 2005) 38

In re Zoloft,
26 F. Supp. 3d 449 (E.D. Pa. 2014).....31

STATUTES, RULES & REGULATIONS

Fed. R. Evid. 702 .....1, 4, 19

OTHER AUTHORITIES

I. Hujoel et al., "Sprue-Like Enteropathy Associated with Olmesartan: A New Kid on the Enteropathy Block," *GE Port. J. Gastroenterol.* (2016).....6

A. Rubio-Tapia et al., "Severe Spruelike Enteropathy Associated With Olmesartan," *Mayo Clin. Proc.* (Aug. 2012).....5, 33

AK Cartee et al., "Sprue-Like Enteropathy Associated With Olmesartan," *Current Cardiovascular Risk Reps.*(2014).....14

Annual Adverse Drug Experience Report: 1996, Surveillance and Data Processing Branch, Division of Pharmacovigilance and Epidemiology, Office of Epidemiology and Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration (Oct. 30, 1997) 35

B. Jabri et al., "IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction," *Nat. Rev. Immunol.* (2015) 32

EV Marietta et al., "Immunopathogensis of olmesartan-associated enteropathy," *Aliment. Pharmacol. Ther.* (2015) 29, 32

FDA Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment 39

Federal Judicial Center, Reference Manual on Scientific Evidence at 555 (3d ed. 2011) 17

G. Ianiro et al., "Systemic review: Sprue-like enteropathy associated with olmesartan," *Aliment. Phamacol. Ther.* (2014) 14

G. Malamut et al., "Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-celiac villous atrophy," *Expert Rev. of Gastroenterology & Hepatology* (2015) 30

I. Aziz et al., "The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015)," *Gut* (2016) 9

J. Menne et al., "Olmesartan and Intestinal Adverse Effects in the ROADMAP Study," *Mayo Clin. Proc.* (December 2012) 17, 18

M. Basson et al., "Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study," *Gut* (2015) ("Basson Paper") 16, 21

Naranjo Adverse Drug Reaction Probability Scale 39

R. Greywoode et al., "Olmesartan, other anti-hypertensives, and chronic diarrhea among patients undergoing endoscopic procedures; a case control study," *Mayo Clin. Proc.* (Sept. 2014) 20, 21

R. Padwal et al., "Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus," *Hypertension* (May 2014) ("Padwal Paper").....22, 23

S. Lagana et al., "Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers," *Journal of Clinical Pathology* (2015) 21

S Scialom et al., "Gastrointestinal Disorder Associated with Olmesartan Mimics Autoimmune Enteropathy," *PLoS One* (2015).....29

V. Abadie et al., "IL-15: a central regulator of celiac disease immunopathology," *Immunol. Rev.* (2014) ("Abadie Paper") 32, 33

World Health Organization Draft Guidance for Adverse Event Reporting and Learning Systems.....39

PRELIMINARY STATEMENT

Plaintiffs proffer Drs. Daniel Leffler and Benjamin Lebwohl, two gastroenterologists, to opine that olmesartan can cause sprue-like enteropathy, which they call "olmesartan enteropathy." Neither can define that condition with any specificity, and both acknowledge that the science regarding olmesartan and sprue-like enteropathy is not developed. What epidemiology does exist suggests the absence of a causal nexus between olmesartan and sprue-like enteropathy. Nevertheless, Drs. Leffler and Lebwohl launch headlong into opinions that olmesartan can cause sprue-like enteropathy, and thrust upon this Court ill-grounded diagnostic criteria for identifying "olmesartan enteropathy" that are of no real assistance to the trier of fact. Drs. Leffler and Lebwohl's opinions are not rooted in the sort of reliable methods envisioned in Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), and should be excluded.

STATEMENT OF FACTS

The Defendants incorporate by reference here the Statement of Facts in the *Daubert* challenge brief as to Dr. Hutfless.

LEGAL ARGUMENT

Drs. Leffler and Lebwohl contend that scientific evidence supports a causal relationship between olmesartan and sprue-like enteropathy. Yet both routinely eschew the limitations of existing studies on which they rely, ignore or downplay

available science, and improperly fill gaps in the scientific record concerning olmesartan with speculation or findings related to entirely different conditions (most prominently, celiac disease). These are not the "good grounds" upon which expert opinion is supposed to be based. *See Daubert*, 509 U.S. at 590.

To be reliable, expert evidence must rest on "the methods and procedures of science" and not "subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 (3d Cir. 1994). "*Daubert*'s requirement that the expert testify to scientific knowledge—conclusions supported by good grounds for each step in the analysis—means that *any* step that renders the analysis unreliable under the *Daubert factors renders the expert's testimony inadmissible.*" *Id.* at 745 (emphasis in original). Drs. Leffler and Lebwohl's methods fail at multiple points:

Both admit that the science regarding this putative condition is new and undeveloped. Rather than be restricted by the state of scientific knowledge, they cobble together every conceivable symptom or sign of gastrointestinal disease and declare that olmesartan can cause them. Their approach has not been peer reviewed, and finds no general acceptance in peer reviewed literature. *See Daubert*, 509 U.S. at 593-94 (peer review and general acceptance are hallmarks of reliability). Absent such grounding, their causation opinions should be rejected. *See* Section I *infra*.

Drs. Leffler and Lebwohl improperly discount the weight of available

epidemiology to mine from the single epidemiological study aligned with their causation opinions. In their determination to grasp whatever epidemiological support exists, they ignore the limitations of that lone study. That is not scientific. *See, e.g.*, *Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 596 (9th Cir. 1996) (unreliable "to 'pick and chose' [sic] from the scientific landscape and present the Court with what he believes the final picture looks like. This is hardly scientific."). *See* Section II *infra*.

There is no evidence of a dose response relationship between olmesartan and sprue-like enteropathy, but Drs. Leffler and Lebwohl speculate as to one anyway and attempt to fill the void in scientific literature with additional speculation that patients taking olmesartan are subject to an increased risk over time. Such speculation should be excluded. *See, e.g.*, *Concord Boat Corp. v. Brunswick Corp.*, 207 F.3d 1039, 1057 (8th Cir. 2000) (quoting *Weisgram v. Marley Co.*, 528 U.S. 440, 454 (2000)) ("Expert testimony that is speculative is not competent proof and contributes 'nothing to a legally sufficient evidentiary basis'"). *See* Section III *infra*.

Drs. Leffler and Lebwohl take data from inconclusive studies to contend that a plausible biological mechanism exists to explain how olmesartan can cause sprue-like enteropathy, but ignore data contrary to their opinions and improperly analogize the experience of celiac patients. That kind of ends-driven and selective

data mining is not reliable methodology. *See, e.g.*, *Miller v. Pfizer, Inc.*, 356 F.3d 1326, 1331, 1335 (10th Cir. 2004) ("selective reliance" on certain evidence to the exclusion of other evidence is "not a generally accepted methodology"). *See* Section IV *infra*.

Drs. Leffler and Lebwohl routinely refer to case reports and adverse event reports, but those reports cannot reliably support general causation opinions. "Neither case reports nor adverse drug reaction reports contain scientific analysis with the safeguards of a controlled experiment. . . . [T]hey reflect reported data, not scientific methodology." *Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999). Even if they could, their methodology for reviewing such evidence is flawed. *See* Section V *infra*.

In short, Drs. Leffler and Lebwohl's opinion that olmesartan can cause sprue-like enteropathy is simply unreliable and should thus be excluded. Fed. R. Evid. 702.

I. DRS. LEFFLER AND LEBWOHL'S OPINION THAT OLMESARTAN CAN CAUSE SPRUE-LIKE ENTEROPATHY IS NOT GROUNDED IN EXISTING SCIENCE

Drs. Leffler and Lebwohl cannot define sprue-like enteropathy with any specificity, and yet contend that olmesartan can cause sprue-like enteropathy – whatever the definition. Their view of the condition is so broad and uncertain that their general causation opinions lack any real foundation. To Drs. Leffler and

Lebwohl, sprue-like enteropathy has countless subjective and objective features of infinite variation in severity, and can be diagnosed upon the presentation of any one of those features no matter how faint. Their opinions go well beyond anything found in the medical literature, and should be barred.

Substantive discussion of an association between olmesartan and sprue-like enteropathy first appeared in the medical literature in 2012. *See* Exhibit A to the Certification of Daniel B. Carroll, Esq. ("Carroll Cert."), A. Rubio-Tapia et al., "Severe Spruelike Enteropathy Associated With Olmesartan," *Mayo Clin. Proc.* at 732-738 (Aug. 2012) ("Rubio-Tapia Paper"); *accord* Carroll Cert., Exhibit B Transcript of the Deposition of Daniel Leffler, M.D. ("Leffler Dep.") at 15:18-17:5. Physicians from the Mayo Clinic described the clinical features of "spruelike enteropathy associated with olmesartan":

TABLE 3. Clinical Features of Spruelike Enteropathy Associated With Olmesartan
Gastrointestinal symptoms (eg, chronic diarrhea, weight loss, steatorrhea)
Negative IgA tissue transglutaminase antibodies (or endomysial antibodies)
Evidence of enteropathy (villous atrophy) with or without collagen deposition or intraepithelial lymphocytosis
Lack of clinical response to gluten exclusion
Exclusion of other causes of enteropathy (eg, celiac disease)
Evidence of clinical and histologic improvement after suspension of olmesartan

Mayo Clinic 2012 at 737. Their views have not changed in the intervening years. *See* Carroll Cert., Exhibit C, I. Hujoel et al., "Sprue-Like Enteropathy Associated with Olmesartan: A New Kid on the Enteropathy Block," *GE Port. J. Gastroenterol.* at 61-65 (2016). These symptoms are objective. As described below, Drs. Leffler and Lebwohl's definition lacks such objectivity.

Drs. Leffler and Lebwohl would have this Court expand the clinical features of sprue-like enteropathy *associated* with olmesartan beyond recognition. Neither have said with any specificity what he thinks olmesartan causes. Instead, they claim that "there are a number of both signs and symptoms across a spectrum of several different axes, including clinical, histopathological, and other signs in terms of laboratory abnormalities. . . . There's no one uniform set of strict criteria that's been developed and there does appear to be a spectrum of abnormalities on all of these axes." Carroll Cert., Exhibit D, Deposition of Benjamin Lebwohl, M.D. ("Lebwohl Dep.") at 253:11-20; *see also* Exhibit B, Leffler Dep. at 72:3-19 ("So I don't think there's any symptom specifically that's necessary for the condition"); Exhibit E, Report of Benjamin Lebwohl, M.D. ("Lebwohl Rep.") at 5 ("There is not a single invariable presentation for this condition"); Exhibit D, Lebwohl Dep. at 100:4-101:1 ("And I would say there's no one case that is the platonic ideal of olmesartan enteropathy, but there are various features that have been reported").

Perhaps to include every plaintiff on the docket here, Drs. Leffler and

Lebwohl posit an open-ended list of subjective and objective non-specific features of "olmesartan enteropathy" that include, but are not limited to: dehydration; "other malabsorptive symptoms"; chronic diarrhea; "alternating bowel habits"; fecal incontinence; constipation; vomiting; weight loss; abdominal pain; nausea; fatigue; "related systemic effects"; "skin changes related to vitamin deficiencies"; bone loss; partial or total villous atrophy; "extra intestinal manifestations"; increased epithelial lymphocytes; and microscopic colitis. *See* Carroll Cert., Exhibit B, Leffler Dep. at 17:6-21:1, 37:12-38:3, 71:10-72:19; Exhibit E, Lebwohl Rep. at 5; Exhibit D, Lebwohl Dep. at 116:19-128:2. According to them, no combination of these features is required – any one of them will do so long as the patient has taken olmesartan. *See* Carroll Cert., Exhibit B, Leffler Dep. at 18:4-17, 45:9-21; Exhibit D, Lebwohl Dep. at 279:23-280:22. No specific level of severity is required; even "mild" symptoms count. *See, e.g.*, Carroll Cert., Exhibit D, Lebwohl Dep. at 378:23-379:15. And, contrary to the *Mayo* case series report, it does not matter how long the patient has taken olmesartan before these symptoms appear. *See, e.g.*, Carroll Cert., Exhibit B, Leffler Dep. at 54:8-16.

The shared inability of Drs. Leffler and Lebwohl to define the condition they claim is caused by olmesartan bespeaks the dearth of scientific evidence supporting their opinion. What Dr. Leffler and Lebwohl have done is to simply proclaim a causal nexus, in contravention of "the ever-present scientific practice to avoid

confusing correlation with causation." Carroll Cert., Exhibit E, Lebwohl Rep. at 29. The courtroom is not the place to develop the scientific record. *See Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151 (E.D. La. 1997) (opinion unreliable where "clinical symptoms he associates with SCD are so varied and general they cannot be corralled into a specific diagnostic criteria").

This proceeding "must function in the present assessing evidence that presently exists." *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003). Drs. Leffler and Lebwohl's effort is manifestly contrary to that mandate. In that Drs. Leffler and Lebwohl contend that olmesartan causes a condition so broadly defined as to find no resonance in the medical literature, their opinions lack foundation and should be excluded. *See, e.g.*, *Daubert*, 509 U.S. at 593-94 (peer review and general acceptance are hallmarks of reliability); *Kilpatrick v. Breg, Inc.*, No. 08-10052-CIV, 2009 WL 2058384, at *4 (S.D. Fla. June 25, 2009) (excluding general causation testimony because the witness "concedes that the medical literature supporting his claim is still a 'developing science'"), Carroll Cert., Exhibit AA.

Drs. Leffler and Lebwohl's frolic also lacks the objectivity required of expert methodology. Both admit that they approached the scientific record with the preconceived conclusion that olmesartan can cause sprue-like enteropathy. *See* Carroll Cert., Exhibit B, Leffler Dep. at 29:3-11 ("I and many of my colleagues

became convinced that this was a true clinical entity" in 2012); Exhibit D, Lebwohl Dep. at 61:8-13 ("And until I read expert reports from the defendants' side and until I started reviewing depositions, I had no idea that there were people who denied the existence of olmesartan enteropathy"). "Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method." *Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502 (9th Cir. 1994).

Drs. Leffler and Lebwohl's unmoored description of sprue-like enteropathy associated with olmesartan leadsthem to additional unsupportable opinions: (1) that "olmesartan enteropathy" is underdiagnosed, and (2) that "olmesartan enteropathy" can be diagnosed by simply monitoring for improvement upon cessation of the drug. As set forth below, neither opinion passes *Daubert* muster. Further, to the extent they are including ordinary diarrhea, abdominal pain and/or vomiting into their definition, those conditions in association with the use of olmesartan have been in the label for years.

A. Speculation Concerning Misdiagnosis/Underdiagnosis.

The published literature describes serious gastrointestinal events associated with olmesartan as rare. *See, e.g.*, Carroll Cert., Exhibit F, I. Aziz et al., "The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-

2015)," *Gut* at 1-10 (2016) (characterizing gastrointestinal disease associated with olmesartan patients as "rare adverse events"); *accord* Exhibit D, Lebwohl Dep. at 269:2-3 (labeling "olmesartan enteropathy" as a "relative rarity"). But Drs. Leffler and Lebwohl contend that "olmesartan enteropathy" "has been misdiagnosed, most often as celiac disease in many patients, or other inflammatory disorders due to the similar clinical presentations, and a lack of knowledge about olmesartan in the medical community." Carroll Cert., Exhibit E, Lebwohl Rep. at 5-6; *see also* Exhibit D, Lebwohl Dep. at 178:5-9 (same); Exhibit B, Leffler Dep. at 24:6-25:5 (same), 124:20-125:1 (speculating "it could be easily underdiagnosed as much as rare"). Neither has done a survey to support this opinion, and the opinion is grounded only in their own purported misdiagnoses of patients and ruminations about misdiagnosis in published literature. *See, e.g.*, Carroll Cert., Exhibit E, Lebwohl Rep. at 5-7. Such speculation is inadmissible. *Accord In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1069 (D. Minn. 2007) (excluding proffered opinion on "what other physicians knew or would have done with different information").

B. Unsupported and Uncertain Diagnostic Criteria

For Drs. Leffler and Lebwohl, any sign or symptom consistent with gastrointestinal disease in patients taking olmesartan may indicate "olmesartan enteropathy." Both have presented diagnostic criteria to determine whether such putative indications are caused by olmesartan, but those criteria are so malleable as

to have no real meaning. As a result, they lack the requisite fit to be aired to a jury or to be relied upon for specific causation opinions—morphed here into general causation opinions – and are not adequately supported in known science.

Lacking clear diagnostic criteria, Drs. Leffler and Lebwohl focus on vaguely-defined and totally subjective "dechallenge evidence" to diagnose "olmesartan enteropathy." "A test is a 'dechallenge' test when a drug that is suspected of causing a certain reaction is withheld to see if the reaction dissipates." *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1999 (11th Cir. 2002). If the reaction dissipates, it is a "positive dechallenge." But even with a positive dechallenge, the cause of the reaction may not have been the drug. *See, e.g.*, *Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1234 n.10 (W.D. Okla. 2000) (positive dechallenges are not reliable evidence of causation; citing dechallenge report where cause may have been idiosyncratic, not drug-induced). Stronger evidence of causation is found when a positive rechallenge occurs – that is, when the drug is reintroduced after a positive dechallenge, and the same reaction re-occurs. *See Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990-91 (8th Cir. 2001).

Drs. Leffler and Lebwohl stray from these diagnostic tools here. "When patients have a clinical response to olmesartan withdrawal, then there is no reason to do an extensive evaluation for other causes because they've already clinically

responded." Carroll Cert., Exhibit B, Leffler Dep. at 244:15-19; *see also* Exhibit D, Lebwohl Dep. at 166:8-167:18 (dechallenge almost always linchpin for causal determination). In other words, they assert that a positive dechallenge is enough, and treating physicians need not do more to assume that olmesartan, and not something else, caused the reaction. For Drs. Leffler and Lebwohl, *any* improvement of *any* of the symptoms *at any time* after withdrawal from olmesartan transforms a potential association into a cause-effect relationship, regardless of other potential causes of the condition. Carroll Cert., Exhibit D, Lebwohl Dep. at 167:10-18 ("Dechallenge involves withdrawal of the offending agent and it involves a change in those various parameters for the better, though there's not a definitive parameter that is essential"), 175:8-20 ("It's hard to be dogmatic about a cutoff" for time to improve); Exhibit B, Leffler Dep. at 59:4-60:10 ("it's hard to make a single rule for how much improvement you need [upon dechallenge] 'cause the clinical presentation can be so different"), 61:6-63:24 (no defined timeframe for improvement upon dechallenge). For Drs. Leffler and Lebwohl, objective evidence is not required to rule out other causes or pin the cause on olmesartan. *See, e.g.*, Carroll Cert., Exhibit B, Leffler Dep. at 74:25-75:22 (biopsy evidence "helpful" but not needed); Exhibit D, Lebwohl Dep. at 317:8-318:13 (biopsy evidence not needed). A rechallenge, though "compelling," also is not needed. *See* Carroll Cert., Exhibit B, Leffler Dep. at 261:24-262:12; Exhibit D, Lebwohl Dep.

at 165:18-166:7. Nor is complete resolution of symptoms upon dechallenge. *See* Carroll Cert., Exhibit B, Leffler Dep. at 55:18-56:9, 57:21-58:3; Exhibit D, Lebwohl Dep. at 167:10-18, 175:8-15. Indeed, a patient need not actually improve in order for Drs. Leffler and Lebwohl to diagnose "olmesartan enteropathy"—only patient reporting of improvement is needed. *See* Carroll Cert., Exhibit D, Lebwohl Dep. at 290:20-291:22 (clinical improvement does not necessarily correlate with histologic improvement); Exhibit B, Leffler Dep. at 59:4-60:10 (threshold for improvement upon dechallenge informed by self-reporting).

Such criteria elevate olmesartan to a presumptive cause, supplanting any reasoned process or objective guideline for diagnosis. Drs. Leffler and Lebwohl encourage the sort of analytical leap that may meet the exigencies of the moment in the clinic, but that is not the stuff of expert testimony in a court of law. *See Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1205-07 (8th Cir. 2000) (excluding opinion that "did not systematically rule out all other possible causes" and "was clearly more concerned with identifying and treating [the plaintiff's] condition than he was with identifying the specific substance that caused her condition").

Indeed, their diagnostic criteria guarantee inconsistent and non-reproducible evaluations of causation evidence. *See* Carroll Cert., Exhibit D, Lebwohl Dep. at 244:22-245:5 ("And it's very possible for two groups of investigators to be encountering the same emerging clinical condition, but to characterize either the

presence or absence of a response somewhat differently and particularly in the absence of some sort of disease assessment score"). The criteria accordingly lack the requisite fit to present to a jury. *See Paoli*, 35 F.3d at 742-43 (the *Daubert* "fit" requirement "requires a valid *scientific* connection to the pertinent inquiry as a precondition to admissibility.") (quoting *Daubert*, 509 U.S. at 591-92)).

Moreover, the criteria proposed by Drs. Leffler and Lebwohl are neither peer reviewed nor supported in the literature, and should be excluded for that reason as well. *Compare, e.g.*, Carroll Cert., Exhibit G, G. Ianiro et al., "Systemic review: Sprue-like enteropathy associated with olmesartan," *Aliment. Phamacol. Ther*.at 16-23 (2014) (declining to find causation in a case series, requiring rechallenge for that assessment); Exhibit H, AK Cartee et al., "Sprue-Like Enteropathy Associated With Olmesartan," *Current Cardiovascular Risk Reps.* at 1-8 (2014) (symptoms "tend to resolve quickly"). Anecdotal approaches to evaluating causation are not reliable bases upon which to ground expert opinion. *See Turner*, 229 F.3d at 1205-07.

To the extent that Drs. Leffler and Lebwohl are attempting to substitute their own application of these criteria to adverse event reports and case reports in the place of a reasoned and reliable general causation opinion (*see* Section V *infra*), that attempt should not be sanctioned by the Court. A differential diagnosis presumes general causation; it does not establish general causation:

> Differential diagnosis may be utilized by a clinician to determine what recognized disease or symptom the patient has, but it is incapable of determining whether the exposure to a substance . . . caused disease in the legal sense. Simply put, an untested hypothesis cannot be a scientifically reliable basis for an opinion on causation.

Lennon v. Norfolk & W. Ry. Co., 123 F. Supp. 2d 1143, 1154 (N.D. Ind. 2000).

* * *

> "Proposed testimony must be supported by appropriate validation –*i.e.*, 'good grounds,' based on what is known . . . ."

Daubert, 509 U.S. at 590. Drs. Leffler and Lebwohl's opinion that olmesartan causes sprue-like enteropathy is not grounded in the existing medical or scientific literature, and should thus be barred.

II. DRS. LEFFLER AND LEBWOHL IMPROPERLY DUCK THE WEIGHT OF EPIDEMIOLOGICAL DATA.

Five epidemiological studies have been published, four showing no statistically significant relationship between olmesartan and sprue-like enteropathy (or symptoms of the same). Drs. Leffler and Lebwohl, of course, rely on the single outlier. *See* Carroll Cert., Exhibit I, Report of Daniel Leffler, M.D. ("Leffler Rep.") at 21-22; Exhibit E, Lebwohl Rep. at 18-19. "Cherry-picking" studies that support an opinion and rejecting contradictory evidence "is not 'good science;' it is therefore inadmissible." *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007).

In 2015, an analysis of a French database study concluded that "olmesartan

users were found to have an increased risk of hospitalization for intestinal malabsorption and coeliac disease compared with [ACE inhibitors].” Carroll Cert., Exhibit J, M. Basson et al., “Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study,” *Gut* at 1-6 (2015) (“Basson Paper”). This retrospective study – the only epidemiological support for Drs. Leffler and Lebwohl’s causation opinions – involved a search of records using predetermined criteria. *See id.* The study presumed that “olmesartan enteropathy” exists; it did not set out to prove its existence. *See* Carroll Cert., Exhibit D, Lebwohl Dep. at 114:11-115:19. By its very nature, the study is susceptible to bias. Indeed, the authors acknowledge potential biases in the data. *See* Carroll Cert., Exhibit J, Basson Paper. For example, the study considered a database of over four million people, yet could only identify a very small incidence (48 cases) of malabsorption. *See id.* Further, the study did not control for concurrent medications, a confounding factor in assessing a relationship between olmesartan and such symptoms. *See id.*

Notwithstanding these limitations, Drs. Leffler and Lebwohl push the Basson study full throttle while improperly discarding every other epidemiological study available. This is not proper expert methodology. *See Lust*, 89 F.3d at 596 (rejecting methodology of “pick[ing] and [choos[ing] from the scientific landscape”). Indeed, none of the other epidemiological evidence supports Drs.

Leffler and Lebwohl's opinion that olmesartan causes sprue-like enteropathy:

A. The ROADMAP Study.

The ROADMAP study was the largest prospective, randomized, double-blind trial of olmesartan. *See* Carroll Cert., Exhibit K, J. Menne et al., "Olmesartan and Intestinal Adverse Effects in the ROADMAP Study," *Mayo Clin. Proc.* at 1230-1232 (December 2012) ("Menne Paper"). Researchers studied high-dose olmesartan, once daily in 2,232 patients treated for a median of 3.2 years. *Id.* Such a study is considered the gold standard in the hierarchy of scientific evidence. *See* FJC, Reference Manual on Scientific Evidence at 555 (3d ed. 2011) (randomized controlled trials are the "gold standard" and "the best way to ensure that any observed difference between the two groups in outcome is likely to be the result of exposure to the drug"). Drs. Leffler and Lebwohl dismiss it, however, claiming ROADMAP was "underpowered" to identify symptoms of enteropathy. *See, e.g.*, Carroll Cert., Exhibit I, Leffler Rep. at 19-20; Exhibit E, Lebwohl Rep. at 4, 13-15.

Though ROADMAP focused on efficacy, researchers collected adverse event data, including data concerning gastrointestinal adverse effects:

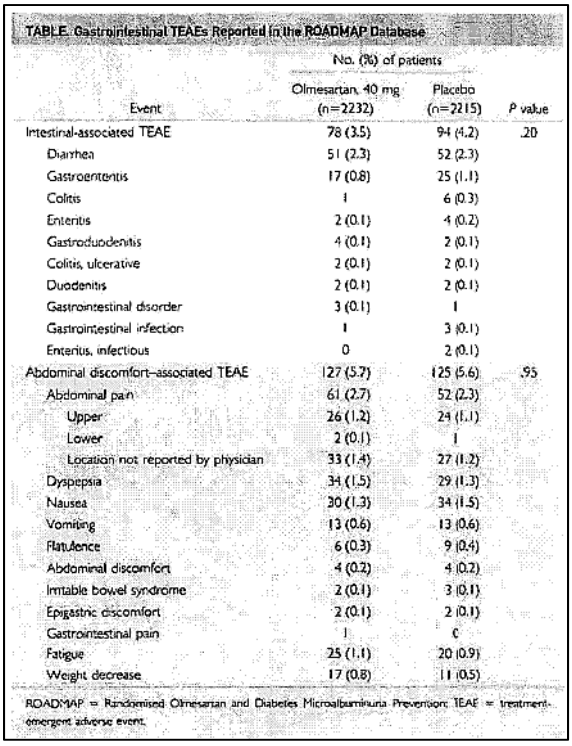

TABLE. Gastrointestinal TEAEs Reported in the ROADMAP Database

Event	No. (%) of patients: Olmesartan, 40 mg (n=2232)	Placebo (n=2215)	P value
Intestinal-associated TEAE	78 (3.5)	94 (4.2)	.20
Diarrhea	51 (2.3)	52 (2.3)	
Gastroenteritis	17 (0.8)	25 (1.1)	
Colitis	1	6 (0.3)	
Enteritis	2 (0.1)	4 (0.2)	
Gastroduodenitis	4 (0.1)	2 (0.1)	
Colitis, ulcerative	2 (0.1)	2 (0.1)	
Duodenitis	2 (0.1)	2 (0.1)	
Gastrointestinal disorder	3 (0.1)	1	
Gastrointestinal infection	1	3 (0.1)	
Enteritis, infectious	0	2 (0.1)	
Abdominal discomfort–associated TEAE	127 (5.7)	125 (5.6)	.95
Abdominal pain	61 (2.7)	52 (2.3)	
Upper	26 (1.2)	24 (1.1)	
Lower	2 (0.1)	1	
Location not reported by physician	33 (1.4)	27 (1.2)	
Dyspepsia	34 (1.5)	29 (1.3)	
Nausea	30 (1.3)	34 (1.5)	
Vomiting	13 (0.6)	13 (0.6)	
Flatulence	6 (0.3)	9 (0.4)	
Abdominal discomfort	4 (0.2)	4 (0.2)	
Irritable bowel syndrome	2 (0.1)	3 (0.1)	
Epigastric discomfort	2 (0.1)	2 (0.1)	
Gastrointestinal pain	1	0	
Fatigue	25 (1.1)	20 (0.9)	
Weight decrease	17 (0.8)	11 (0.5)	

ROADMAP = Randomised Olmesartan and Diabetes Microalbuminuria Prevention; TEAE = treatment-emergent adverse event.

Carroll Cert., Exhibit K, J. Menne Paper. They reported that "in more than 2200 patients taking high-dose olmesartan for more than 3 years, we did not observe an intestinal effect of olmesartan." *Id.*

According to Drs. Leffler and Lebwohl, because ROADMAP did not specifically key in on gastrointestinal disease as a sole focus from the outset, its data can be ignored. *See* Carroll Cert., Exhibit I, Leffler Rep. at 19-20; Exhibit B, Leffler Dep. at 282:1-20; Exhibit E, Lebwohl Rep. at 4, 13-15; Exhibit D, Lebwohl Dep. at 231:10-12, 372:17-374:14. They would rather turn the hierarchy of scientific evidence on its head: "For secondary outcomes and adverse events, [randomized controlled trials] are often insufficient. And this is why we do things like MedWatch reports, 'cause even in the largest clinical trial, randomized clinical

trial, pivotal clinical trial, uncommon and unexpected adverse events are often not seen." Carroll Cert., Exhibit B, Leffler Dep. at 282:15-20. Their analysis does not meet the requirements of Rule 702 and *Daubert*. *See Meister v. Med Eng'g Corp.*, 267 F.3d 1123, 1131-32 (D.C. Cir. 2001) (affirming exclusion of plaintiff's expert in breast implant case who relied on case reports over epidemiologic evidence).

And their criticism is unfounded. Indeed, Dr. Leffler contends that an adverse event report submitted in connection with the ROADMAP study supports his opinion that olmesartan can cause sprue-like enteropathy. *See* Carroll Cert., Exhibit I, Leffler Rep. at 16 (describing an adverse event report collected in connection with the ROADMAP study as supportive of his general causation opinion). And plaintiffs' putative regulatory causation expert Dr. David Kessler contends that adverse event reports from ROADMAP constituted information that should have signaled to Daiichi Sankyo a need to investigate the association between olmesartan and sprue-like enteropathy further. *See* Carroll Cert., Exhibit L, Deposition of David Kessler, M.D. ("Kessler Dep.") at 249:9-22 (contending Daiichi Sankyo could have conducted further investigation of adverse events generated during the ROADMAP study). If discovery of such information is "why we do things like MedWatch reports," the ROADMAP study covered that base.

Drs. Leffler and Lebwohl cannot have it both ways: either the ROADMAP study was "underpowered," or it generated data that inform the existence or

absence of a causal association between olmesartan and sprue-like enteropathy. Their dismissal of epidemiological data derived from this study, while relying on the same data for cherry-picked adverse event anecdotes, underscores the ends-driven analysis in which these putative experts engaged in forming their opinions. Such methodology is not reliable and should be rejected. *Miller*, 356 F.3d at 1331, 1335 ("selective reliance" on certain evidence to the exclusion of other evidence is "not a generally accepted methodology").

B. <u>The Greywoode Study.</u>

A univariate and multivariate analysis by Greywoode et al. – of which Dr. Lebwohl was a co-author – was published in 2014, apparently before Dr. Lebwohl was retained as a litigation expert by the plaintiffs. Carroll Cert., Exhibit M, R. Greywoode et al., "Olmesartan, other anti-hypertensives, and chronic diarrhea among patients undergoing endoscopic procedures; a case control study," *Mayo Clin. Proc.* at 1239-1243 (Sept. 2014). The study was prompted by reports in the medical literature of an association between olmesartan and sprue-like enteropathy. *See id.* Researchers looked at data from 14,516 patients undergoing endoscopic procedures for diarrhea, and "found neither olmesartan nor other [angiotensin receptor blockers] were associated with diarrhea" among these patients. *Id.*

Drs. Lebwohl and Leffler, as litigation experts, now discount this study because only 105 patients studied had been exposed to olmesartan. See Carroll

Cert., Exhibit I, Leffler Rep. at 23; Exhibit E, Lebwohl Rep. at 15-16; Exhibit D, Lebwohl Dep. at 156:17-158:12. The number of olmesartan patients studied did not impair the ability to make observations concerning the statistical significance of a drug effector for Dr. Lebwohl from reaching the conclusions shared in the article. And, just as the Basson study, the Greywoode paper was peer-reviewed. For opinions to be admissible, experts must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). The only explanation for discounting statistically significant epidemiological data is that Drs. Leffler and Lebwohl find that data inconvenient now that they are litigation experts for the plaintiffs. Such rationale for ignoring epidemiological data is devoid of the "intellectual rigor" required of experts.

C. The Lagana Study

A cohort study co-authored by, among others, two of plaintiffs' general causation experts (Dr. Lebwohl and Dr. Stephen Lagana) evaluated whether histopathologic changes could be seen in patients experiencing sprue-like symptoms while taking olmesartan. Carroll Cert., Exhibit N, S. Lagana et al., "Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers," *Journal of Clinical Pathology* at 29-32 (2015). This study also was prompted by case reports associating olmesartan and

sprue-like enteropathy, but here too researchers did not identify a statistically significant difference between olmesartan patients and non-olmesartan patients. *See id.*

Drs. Leffler and Lebwohl – now as litigation experts – sweep aside this finding because the study was "likely underpowered." Carroll Cert., Exhibit E, Lebwohl Rep. at 16. However, they betray that rationale by highlighting a non-statistically significant "trend" noted by the authors toward enteropathy in olmesartan users. *See id.*; Exhibit I, Leffler Rep. at 24; Exhibit B, Leffler Dep. at 301:8-22. Dr. Leffler concedes that the "trend" he and Dr. Lebwohl highlight is skewed by the methods of the investigators of that study. Carroll Cert., Exhibit B, Leffler Dep. at 302:1-307:3. Reliable methodology does not ignore statistically significant findings butrely on trends that are not statistically significant. *See Caraker v. Sandoz Pharms. Corp*., 188 F. Supp. 2d 1026, 1033-34 (S.D. Ill. 2001) ("reject[ing] the plaintiffs' experts' opinions inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies").

D. <u>The Padwal Study.</u>

A 2014 cohort study conducted by Padwal et al. evaluated the association between olmesartan and gastrointestinal disease-related hospitalization. Carroll Cert., Exhibit O, R. Padwal et al., "Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus," *Hypertension* at 977-

983 (May 2014) ("Padwal Paper"). Like others, the study was prompted by reports associating olmesartan with sprue-like enteropathy. *See id.* Researchers evaluated 45,185 angiotensin receptor blocker patients, 10,370 of whom were taking olmesartan, and found based on "a clinically rich data set . . . that olmesartan use compared with other ARB use was not associated with an increased risk of hospitalization or all-cause mortality in the overall cohort." *Id.* Defendants acknowledge that approximately two and a half years after publication of this study, Dr. Padwal was engaged as an expert in the litigation for the defendants.

Even though the Padwal study is one of only five epidemiological studies available, neither Dr. Leffler nor Dr. Lebwohl sees fit to cite it in his report. *See generally* Carroll Cert., Exhibit I, Leffler Rep.; Exhibit E, Lebwohl Rep. Indeed, Dr. Lebwohl did not even review it in connection with forming the opinions in this case. *See* Carroll Cert., Exhibit D, Lebwohl Dep. at 94:8-15, 98:3-15. Dr. Leffler discredits the Padwal study because, he says, the study population had not had "a significant enough duration of exposure [to olmesartan] to really begin seeing . . . olmesartan enteropathy severe outcome cases." Carroll Cert., Exhibit B, Leffler Dep. at 309:14-310:2. His criticism does not square with his other opinions, however: Dr. Leffler believes that "olmesartan enteropathy" can occur any time after a patient takes his or her first pill. Carroll Cert., Exhibit B, Leffler Dep. at 50:18-52:7. The Padwal study population included only subjects with a minimum

of one year of baseline data, and provided for a maximum follow-up period of six years. Carroll Cert., Exhibit O, Padwal Paper.

Dr. Leffler's internally inconsistent dismissal of the Padwal study and Dr. Lebwohl's failure to consider it demonstrate the unreliable methodology deployed by these doctors in arriving at the opinion that olmesartan causes sprue-like enteropathy. They prefer to "present the Court with what [they] believe[] the final picture looks like," rather than the actual scientific record. *Lust*, 89 F.3d at 596.

* * *

> "Epidemiologic studies are the primary, generally accepted methodology for demonstrating a causal relation between a chemical and the set of symptoms or a disease."

Rains v. PPG Indus., Inc., 361 F. Supp. 2d 829, 836 (S.D. Ill. 2004). Drs. Leffler and Lebwohl's review of epidemiology is nothing more than an ends-driven evaluation determined to support the pre-formed conclusion that olmesartan causes sprue-like enteropathy. Dr. Lebwohl even disavows statistically significant findings *in his own studies* for the purposes of advancing his opinions in this litigation. That reversal is litigation-driven and inexpert. *See, e.g.*, Carroll Cert., Exhibit P, *Carl v. Johnson & Johnson*, No. ATL-L-6546-14 (N.J. Sup. Sept. 2, 2016), slip op. (appeal pending)) at 30 ("Dr. Cramer's methodology appears to be litigation driven rather than objectively and scientifically grounded . . . . In all of his prior peer-reviewed articles, Dr. Cramer never once stated that he believes talc causes ovarian cancer

. . . . In fact, in his study of 2007, he [rejected such a claim]"); *In re Methyl Tertiary Butyl Ether (MTBE) Prods. Liab. Litig.*, 593 F. Supp. 2d 549, 563 (S.D.N.Y. 2008) (excluding opinion where expert was not "as careful as he would be in his regular professional work outside his paid litigation consulting").

As strength of the association between olmesartan and sprue-like enteropathy is an essential factor in their causation opinions, Drs. Leffler and Lebwohl's flawed methodology in evaluating evidence of that factor demonstrates the unreliability of their opinions. *See Paoli*, 35 F.3d at 745 ("*any* step that renders the analysis unreliable . . . *renders the expert's testimony inadmissible*").

III. DRS. LEFFLER AND LEBWOHL CONCEDE THERE IS NO DOSE RESPONSE RELATIONSHIP BETWEEN OLMESARTAN AND GASTROINTESTINAL DISEASE.

Drs. Leffler and Lebwohl admit that there is no data supporting a dose response relationship between olmesartan and the signs and symptoms of what they call "olmesartan enteropathy." *See* Carroll Cert., Exhibit B, Leffler Dep. at 225:15-226:3 ("there's no evidence that there is a dose response that's discernible"); Exhibit D, Lebwohl Dep. at 221:16-22 ("I've not seen such data"). Speculation as to a dose response (*see, e.g.*, Exhibit D, Lebwohl Dep. at 221:16-224:13) should be excluded. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse*

dixit of the expert").

Dose response (biological gradient) is an essential feature of the Bradford-Hill method for assessing causation (*see, e.g.*, Carroll Cert., Exhibit P, *Carl v. Johnson & Johnson*, No. ATL-L-6546-14, slip op.) at 17) – a method both doctors profess to have followed in their assessment of the scientific evidence regarding olmesartan. *See* Carroll Cert., Exhibit I, Leffler Rep. at 11 (identifying Bradford-Hill criteria as central to the causation analysis); Exhibit E, Lebwohl Rep. at 28 (same). Drs. Leffler and Lebwohl gloss over the void in the scientific record concerning biological gradient, and posit that "the risk of olmesartan enteropathy increases with duration of exposure to olmesartan." Carroll Cert., Exhibit I, Leffler Rep. at 13. This opinion is rank speculation and should be excluded. *See Gen. Elec.*, 522 U.S. at 146.

As a preliminary matter, neither Dr. Leffler nor Dr. Lebwohl can state why such an "increased risk" occurs. They resort instead to guesswork. Both contend that extended exposure to olmesartan presents an "increased risk" because of either a "cumulative dose effect . . . or a second environmental trigger." Carroll Cert., Exhibit I, Leffler Rep. at 13; *see also* Exhibit D, Lebwohl Dep. at 67:2-14 ("there does appear to require either some sort of cumulative effect of damage or some sort of priming of the immune system or some cofactor . . . as yet unidentified"). But neither cites any studies establishing a cumulative dose effect or a second

environmental trigger effect with olmesartan. *Cf.* Carroll Cert., Exhibit B, Leffler Dep. at 52:12-54:1 (speculating on the cause of variation of temporal onset of symptoms); Exhibit D, Lebwohl Dep. at 71:12-73:22 (same). Accordingly, such opinions should be barred. *See United Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 528 (W.D. Pa. 2003) (excluding expert opinions where "[t]he body of scientific evidence . . . is simply insufficient to support a scientifically reliable application of plaintiff's experts' methodology").

Moreover, neither Dr. Leffler nor Dr. Lebwohl can define the timeframe for this putative increased risk. *See, e.g.*, Carroll Cert., Exhibit B, Leffler Dep. at 50:5-51:13 (published reports of sprue-like enteropathy associated with olmesartan range from weeks to years after initiation of the drug); Exhibit E, Lebwohl Rep. at 18-19 (describing variation in "delayed onset of olmesartan enteropathy" in the scientific record). Their opinion that risk increases over time is *ipse dixit* – any time a response is seen after the first pill is taken, is fair game for causation. "I think as long as there's continued exposure to the drug, there is no – there's no time at which it is not possible to develop [sprue-like enteropathy]." Carroll Cert., Exhibit B, Leffler Dep. at 54:8-16. There is no support for this opinion in the medical literature, and Dr. Leffler does not refer to any.

Drs. Leffler and Lebwohl's speculation that patients have an increased risk of injury over an amorphous and undefined timeframe should be excluded. "The

courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *See Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

IV. THE MEDICAL LITERATURE DOES NOT SUPPORT A PLAUSIBLE BIOLOGICAL MECHANISM OF ACTION.

Ultimately, neither Dr. Leffler nor Dr. Lebwohl can say how olmesartan affects patients. Carroll Cert., Exhibit D, Lebwohl Dep. at 68:12-69:15 ("[O]lmesartan is what is necessary for developing olmesartan enteropathy, but it might not be sufficient. There might be some other factors that need to be present . . . . we don't yet know what those factors are, but one can speculate" in cases); *id.* at 71:12-73:22 ("I don't think we know enough to be sure yes or no" how olmesartan putatively causes enteropathy in various patients); Exhibit B, Leffler Dep. at 53:13-54:1 (speculating on mechanism of action); *accord* Exhibit E, Lebwohl Rep. at 19 ("the immune response to this medication" is "as-yet fully characterized"). Notwithstanding this concession, Drs. Leffler and Lebwohl opine that there is a mechanism by which olmesartan can cause sprue-like enteropathy, such that the "plausible biological mechanism" criterion of the Bradford-Hill analysis is met. *See* Carroll Cert., Exhibit I, Leffler Rep. at 12-13; Exhibit E, Lebwohl Rep. at 20-21. But this opinion is speculation rooted only in inconclusive observations concerning a small number of olmesartan patients and an incongruous reference to celiac disease literature. This is not well-grounded expert opinion.

Accord Hendrix v. Evenflo Co., 255 F.R.D. 568, 602 (N.D. Fla. 2009) ("what is clear to the court from its review of the record in this case is that 'neither [the expert] nor medical science knows the exact process that results in [autism] or the factors that trigger that process'").

Drs. Leffler and Lebwohl rely principally on three publications relating to olmesartan to support their claim that a plausible biological mechanism exists. *See* Carroll Cert., Exhibit B, Leffler Dep. at 168:18-175:2 (identifying Marietta, Scialom, and Malamut papers as bases for biological mechanism opinion); Exhibit E, Lebwohl Rep. at 20-21 (citing Marietta paper for the same). None of these publications does more than lay the groundwork for future study:

The Marietta paper observed increased IL-15 expression in some olmesartan patients, speculating that "one potential unifying theory . . . is that these patients in certain circumstances were unable to down-regulate the IL-15 expression . . . and therefore later developed enteropathy." The authors noted multiple limitations to their study and the need for "further analysis." *See* Carroll Cert., Exhibit Q, EV Marietta et al., "Immunopathogensis of olmesartan-associated enteropathy," *Aliment. Pharmacol. Ther*. at 1-12 (2015) ("Marietta Paper").

The Scialom paper is a case series relating to seven olmesartan patients, not a study to identify a plausible biological mechanism. Indeed, the authors state clearly: "How olmesartan can induce severe inflammation and intestinal damage

remains to be elucidated." *See* Carroll Cert., Exhibit R, S Scialom et al., "Gastrointestinal Disorder Associated with Olmesartan Mimics Autoimmune Enteropathy," *PLoS One* at 1-9 (2015).

The Malamut paper reviewed literature concerning various enteropathies and noted that the mechanism of action in cases in which sprue-like enteropathy had been associated with olmesartan "remains to be elucidated." *See* Carroll Cert., Exhibit S, G Malamut et al., "Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-celiac villous atrophy," *Expert Rev. of Gastroenterology & Hepatology* at 719-721 (2015).

Drs. Leffler and Lebwohl stretch these papers beyond their inherent limitations, ignoring the caveats specifically called out by the authors. This sort of extrapolation is not a reliable basis upon which to form an expert opinion, and should be rejected. *Glastetter*, 252 F.3d 986, 989-900 (8th Cir. 2001) (excluding expert opinion inappropriately extrapolated from case studies, medical texts, and other sources, where such studies did not explicitly support the opinion).

Rather than acknowledge the inchoate state of science, Drs. Leffler and Lebwohl improperly mine these publications for propositions that they claim support their conclusions – for example, increased IL-15 expression or increased numbers of CD8+ T cells – while ignoring findings that counter their conclusions—for example, no increase in granzyme B positive cells and an

increase in FoxP3 cells. *See* Carroll Cert., Exhibit I, Leffler Rep. at 12-13; Exhibit B, Leffler Dep. at 168:18-175:2; Exhibit E, Lebwohl Rep. at 20-21. This selective data mining is inexpert. *In re Zoloft*, 26 F. Supp. 3d 449, 460-61 (E.D. Pa. 2014) (methodology not reliable where it "selectively discuss[es] studies most supportive of her conclusions . . . and fails to account adequately for contrary evidence"). And it is clearly ends-driven.

Drs. Leffler and Lebwohl pick and choose from the scientific record to forge an artificial analogy between "olmesartan enteropathy" and celiac disease. *See* Carroll Cert., Exhibit B, Leffler Dep. at 162:5-9, 175:3-176:5 (analogizing celiac literature); *see also* Exhibit E, Lebwohl Rep. at 20 (same); Exhibit D, Lebwohl Dep. at 71:12-73:22 (same). The impropriety of this analogy is laid bare by Dr. Leffler.

As a preliminary matter, Dr. Leffler acknowledges important differences between celiac patients and patients experiencing what he terms "olmesartan enteropathy." Carroll Cert., Exhibit I, Leffler Rep. at 10; Exhibit B, Leffler Dep. at 168:18-175:2. Of particular importance, it is well-known how gluten is processed by immune cells and the cell damage that occurs in celiac disease as a result of ingesting gluten. *See* Carroll Cert., Exhibit D, Lebwohl Dep. at 67:20-69:15 (distinguishing between what is known about mechanism for celiac disease versus the same for "olmesartan enteropathy"). The same level of knowledge does not

exist with respect to how olmesartan is processed. *See id.*

In any event, Dr. Leffler claims (as does Dr. Lebwohl) that an increase in IL-15 expression, as reported in the Marietta Paper (Carroll Cert., Exhibit Q), leads to a "destructive" T cell response. *See* Carroll Cert., Exhibit I, Leffler Rep. at 12. The T cell response side of this equation, however, has no support in the scientific record relating to olmesartan. Rather, that comes from celiac literature. Carroll Cert., Exhibit I, Leffler Rep. at 12 (citing B. Jabri et al., "IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction," *Nat. Rev. Immunol.* at 771-83 (2015)). The analogy to celiac disease, however, is inapposite.

Indeed, celiac literature does not support Dr. Leffler's opinion: Whereas the Marietta paper found increased IL-15 expression only in the epithelium (the outer layer of the intestine), celiac-related villous atrophy occurs only when patients experience IL-15 expression in the epithelium *and* the lamina propria (the layer under the epithelium). *Compare* Carroll Cert., Exhibit Q, Marietta Paper, *with* Exhibit T, V. Abadie et al., "IL-15: a central regulator of celiac disease immunopathology," *Immunol. Rev.* at 221-234 (2014) ("Abadie Paper"). In celiac disease, IL-15 expression in the epithelium only (what the Marietta paper observed) is *not* sufficient to cause villous atrophy. *See id*. But Dr. Leffler is willing to ignore the distinction for the sake of his opinion here, and speculates that IL-15 in the epithelium alone suffices as a mechanism by which olmesartan can

cause sprue-like enteropathy. *See* Carroll Cert., Exhibit B, Leffler Dep. at 179:17-182:23.

Though the disparate scientific materials from which Dr. Leffler derives information have been peer-reviewed, the manner by which he has glued them together to conclude olmesartan can cause sprue-like enteropathy has not. Piecing together building blocks to reach an untested conclusion is not a reliable methodology. *See, e.g., McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1245 (11th Cir. 2005) (attempt to opine on general causation by analogy inexpert where "[t]he medical articles do not support these conclusions" and "[s]peculation replaces science in this unreliable analogy"); *Doe v. Ortho-Clinical Diagnostics, Inc.*, 440 F. Supp. 2d 465, 472-76 (M.D.N.C. 2006) (excluding putative expert with a similar methodology).

Drs. Leffler and Lebwohl's willingness to skew available science and make unsupported leaps is all the more problematic in light of the scientific evidence that they ignored. Indeed, in vitro and in vivo data almost universally reported that olmesartan is anti-inflammatory and anti-fibrogenic. These qualities would tend to temper the clinical and histological features that Drs. Leffler and Lebwohl associate with olmesartan, not cause them. Though the published literature recognizes this data (*see* Carroll Cert., Exhibit A, Rubio-Tapia Paper), Drs. Leffler and Lebwohl do not even address it. *See, e.g.*, Carroll Cert., Exhibit B, Leffler Dep.

at 138:3-6, 192:18-193:20; Exhibit D, Lebwohl Dep. at 59:12-24. This failure to account for this available data is again ends-driven and inexpert. *See Miller*, 356 F.3d at 1331, 1335 ("selective reliance" on certain evidence to the exclusion of other evidence is "not a generally accepted methodology").

Drs. Leffler and Lebwohl should not be permitted to speculate on a plausible biological mechanism by which olmesartan can cause sprue-like enteropathy. Their opinions should be restricted to that which is known: that no plausible biological mechanism has been elucidated.

V. DRS. LEFFLER AND LEBWOHL'S OPINION THAT ADVERSE EVENT REPORTS AND CASE REPORTS SUPPORT GENERAL CAUSATION IS NOT RELIABLE.

"Neither case reports nor adverse drug reaction reports contain scientific analysis with the safeguards of a controlled experiment. . . . they reflect reported data, not scientific methodology." *Brumbaugh*, 77 F. Supp. 2d at 1156; *accord* Carroll Cert., Exhibit D, Lebwohl Dep. at 327:10-12 ("in every MedWatch report you're never going to get the entire story"). Nevertheless, Drs. Leffler and Lebwohl rely substantially on this data to opine that olmesartan can cause sprue-like enteropathy. *See* Carroll Cert., Exhibit I, Leffler Rep. at 14-26; Exhibit E, Lebwohl Rep. at 9-13, 22-23, 30-37. This is not the "good grounds" envisioned by *Daubert*.

Extending adverse event data to make judgments regarding toxicity is not a

generally accepted technique or practice. The FDA has concluded that adverse event data "may not be used to calculate instances or estimates of drug risk." Carroll Cert., Exhibit U, Annual Adverse Drug Experience Report: 1996, Surveillance and Data Processing Branch, Division of Pharmacovigilance and Epidemiology, Office of Epidemiology and Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration (Oct. 30, 1997) at 1. This is because such data are uncertified reports of events that do not necessarily relate to the use of any particular drug. *Id.*; *accord McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005) (adverse event data is "[u]ncontrolled anecdotal information that offers one of the least reliable sources to justify opinions about both general and individual causation"); *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1045 (D.N.J. 1992) (adverse event reports "have inherent biases as they are second-or-third hand reports, are affected by medical or mass media attention, and are subject to other distortions").

Likewise, case reports do not constitute data on which a reliable causation opinion may be formed:

> "[C]ase reports are merely accounts of medical events." A doctor makes a case report when a patient demonstrates adverse symptoms that are temporally connected with the prescribed drug. The reports contain very basic information, often omitting patient histories, descriptions of the course of treatment, and reasoning to exclude other possible causes. "Case reports make little attempt to screen out alternative causes for a patient's

> condition. They frequently lack analysis. And they often omit relevant facts about the patient's condition. Hence, causal attribution based on case studies must be regarded with caution."

Ervin v. Johnson & Johnson, Inc., No. 2:04-cv-0205, 2006 WL 1529582, at *6 (S.D. Ind. May 30, 2006), *aff'd* 492 F.3d 901 (7th Cir. 2007) (internal citations omitted), Carroll Cert., Exhibit BB; *see also Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1361-62 (N.D. Ga. 2001) ("even if relevant case reports existed, they cannot establish general causation: [C]ase reports are not reliable scientific evidence of causation, because they simply describe[] reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; do not isolate and exclude potentially alternative causes; and do not investigate or explain the mechanism of causation").

Both experts overextend information supplied in adverse event reports and case reports and ignore gaps in that information to substantiate their general causation opinions. *See, e.g.*, Carroll Cert., Exhibit B, Leffler Dep. at 218:11-240:17, 246:2-260:21; Exhibit D, Lebwohl Dep. at 328:2-329:13, 341:17-345:4. Indeed, notwithstanding gaps in data, Drs. Leffler and Lebwohl contend that a differential diagnosis can be made from an adverse event report or case report, and that such a diagnosis can substitute for general causation. *See* Carroll Cert., Exhibit B, Leffler Dep. at 200:14-21 ("made a differential" in analyzing adverse event reports); Exhibit D, Lebwohl Dep. at 333:20-22 ("And so a differential can

certainly be applied when reviewing a MedWatch report"). Their opinions are not predicated on reliable methods. *See, e.g.*, *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316 (11th Cir. 1999) ("While we acknowledge the importance of anecdotal studies for raising questions and comparing clinicians' findings, in the face of controlled, population-based epidemiological studies which find otherwise, these case reports pale in comparison").

The fallacy in developing causation opinions based on case report and adverse event data is evident in Dr. Leffler's re-analysis of adverse event data, a science fair exercise run amok as described in more detail in the brief with regard to plaintiffs' putative expert Dr. Susan Hutfless. For the purposes of this litigation, Dr. Leffler was asked to review 62 adverse event reports to assess whether the reported information demonstrated a causal nexus between olmesartan and the reported event. *See* Carroll Cert., Exhibit B, Leffler Dep. at 196:19-199:25. Before this litigation, Dr. Leffler had never reviewed an adverse event report, nor had he ever submitted one. *See id.* at 204:1-6, 205:21-23. Dr. Leffler relied on another of plaintiffs' putative general causation experts, Dr. David Kessler, to select the reports he reviewed. *See id.* at 197:25-198:8. Dr. Leffler had no input in Dr. Kessler's selection method. *See id.* at 198:13-19. And Dr. Leffler did not make any effort to assure himself that the selection of reports he reviewed could be reproduced using the methodology deployed by Dr. Kessler. *See id.* at 199:15-18.

Nevertheless, based on this review, Dr. Leffler concludes that adverse event data support his general causation opinion. Carroll Cert., Exhibit I, Leffler Rep. at 14-18.

A principle methodological flaw in Dr. Leffler's opinions is that Dr. Kessler's selection of adverse event data is not reproducible. Dr. Kessler does not recall the precise date range of or the terms used for the search. *See* Carroll Cert., Exhibit L, Kessler Dep. at 172:12-25, 191:7-22. After an initial cut was made, Dr. Kessler engaged in a clinical assessment to evaluate the "seriousness" and "medical importance" of the reports, and to identify "anything that signaled rechallenge" or "was similar to rechallenge" in the reported narrative. *See id.* at 181:22-183:2, 186:24-188:5, 193:18-194:9. This, even though Dr. Kessler admits that he is not an expert in gastroenterology. *See* Carroll Cert., Exhibit V, Report of David Kessler, M.D. ("Kessler Rep.") at 24. In other words, the selection of data for Dr. Leffler to review was the product of uncertain and subjective criteria applied by a non-expert. For that reason alone, Dr. Leffler's analysis of adverse event reports should be excluded. *See Zenith Elecs. Corp. v. WH-TV Broadcasting Corp.*, 395 F.3d 416, 419 (7th Cir. 2005) ("Someone else using the same data and methods must be able to replicate the result").

Beyond the methodological flaws in data selection, however, Dr. Leffler failed to exercise the requisite scientific rigor in evaluating the data selected. There

are developed frameworks to assist pharmaceutical companies and health agencies in determining if individual cases reflect a "causal" relationship for purposes of reporting and subsequent investigation. *See, e.g.*, Carroll Cert., Exhibit W, Naranjo Adverse Drug Reaction Probability Scale; Exhibit X, World Health Organization Draft Guidance for Adverse Event Reporting and Learning Systems; Exhibit Y, FDA Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Dr. Leffler did not follow those methodologies in evaluating adverse event reports.

For example, those accepted frameworks counsel thorough evaluation of potential alternative causes, such as concurrent medications and co-morbidities. *See id*. Dr. Leffler followed that advice only when it was convenient for him. When evaluation of the 62 adverse event reports revealed information gaps in those areas – for instance, because the reporter did not have that information or refused to provide it—Dr. Leffler filled the gaps by assuming no co-morbidities or concurrent medications. *See* Carroll Cert., Exhibit Z, Deposition of Suzanne Hutfless, M.D. ("Hutfless Dep.") at 140:24-142:17 (describing Dr. Leffler's approach to assessing alternative causes: "Based on our conversation any time something was listed as missing or not mentioned it was no").

The result is an artificial composite more likely to suggest a signal to investigate a potential causation and, for Dr. Leffler, evidence of a causal nexus between olmesartan and sprue-like enteropathy. *See* Carroll Cert., Exhibit B,

Leffler Dep. at 202:24-203:5. This is not the sort of work or opinion that the Court should deem reliable. *Kumho Tire*, 526 U.S. at 152 (requiring that "an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field"). Expert opinion predicated on adverse event reports is not admissible, and running the reports through a Cuisinart as was done here does not change that.

CONCLUSION

For the foregoing reasons, Defendants respectfully submit that Drs. Leffler and Lebwohl should be precluded from offering an opinion on general causation.

Respectfully submitted,

s/ Susan M. Sharko

Susan M. Sharko, Esq.
Michael C. Zogby, Esq.
Daniel B. Carroll, Esq.
DRINKER BIDDLE & REATH LLP
A Delaware Limited Liability Partnership
600 Campus Drive
Florham Park, New Jersey 07932-1047
(973) 549-7000
Attorneys for Defendants Daiichi Sankyo, Inc., Daiichi Sankyo US Holdings, Inc., Daiichi Sankyo Company, Ltd., Forest Laboratories, LLC, Forest Pharmaceuticals, Inc., and Forest Research Institute, Inc.

Dated: March 31, 2017

88199651.1